THE PHYSIOLOGICAL ACTION OF HYOSCYAMINE.

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THE use of hyoscyamine has received a good deal of attention of late, but its physiological action has not been studied; this fact has induced me to undertake the study of its physiological action. An examination of the literature on the subject shows that up to this time our knowledge of its physiological and therapeutical action is quite imperfect, and the statements in regard to it quite conflicting, and mainly based upon its supposed identity with atropia.

Before detailing my own experiments with the alkaloid I shall give a brief sketch of what has been written about it.

After Peschier, in 1821, and Payen, in 1824, had indicated the probable existence of an alkaloid in hyoscyamus niger, Geiger and Hesse (1833) succeeded in extracting pure hyoscyamine. It is found most plentifully in the seeds, in less quantity in the leaves, of hyoscyamus niger and hyoscyamus albus.

According to Geiger, hyoscyamine crystallizes slowly in star or brush-like clusters of silky, sometimes transparent, needles, which have no smell; less pure it forms a viscid amorphous mass, hard to dry, which, as long as it is moist, has a disagreeable, overpowering, tobacco-like odor; it tastes exceedingly acrid and unpleasant. With gentle heat it melts to an oily-like liquid, and evaporates with careful heating, for the most part undecomposed.

Wadgymar states that hyoscyamine with careful heating will sublime unchanged ; by sublimation he obtained white silky needles from 1½ to 2 lines in length.

According to Thorey, hyoscyamine crystallizes out of chloroform in rhombic tables, out of benzole in fine needles, while out of ether and amylic alcohol it remains amorphous. In a pure state it is constant in the air, with difficulty soluble in cold water, more soluble in warm ; impure it is hygroscopic, and much more soluble in water ; it is further soluble in alcohol, ether, chloroform, amylic alcohol, benzole, and diluted acids. Hyoscyamine saturates the acids completely ; its solution in hydrochloric, sulphuric, nitric, phosphoric, and acetic acids give easily and good crystallizing salts. The hydrochloric salt forms cross-like crystals, whilst the rest crystallize in fine straight needles.

The watery solution of the free base decomposes slowly in the air, more rapidly with slight warmth and alkalies, becoming a brown color and developing ammonia.

The action of hyoscyamine, says Wirkung, upon which its medicinal and toxic action seems to rest, is qualitatively similar to that of atropia ; quantitatively, far superior to it, as far as the pupils show on local application, which are more rapidly and persistently dilated. Schroff states that the $\frac{1}{8000}$ grain caused mydriasis in fifteen minutes in an albino rabbit, which reached its maximum in forty minutes and ended in five or six hours, whereas atropine in this solution did not work mydriatically.

Lemettre finds atropia act more powerfully mydriatically than hyoscyamine. In 1825 Reisinger determined the mydriatic action of the still impure hyoscyamine by means of experiments on animals. As regard the remote appearances, according to Schroff, hyoscymine produces only exceptionally the erythema of the skin and scarlatina-like exanthem so frequently brought out by atropine. It does not bring on the furious delirium and the increased restlessness as well as the staggering and muscular weakness which are peculiar to atropine, or only after very large doses; on the contrary, there are rest and sleep, and finally no paralysis of the bladder and anus. Whether these differences in the action of hyoscyamine and atropine do not partially rest upon individual peculiarities, we do not dare to decide, although the experiments which Frommüller made on patients with hyoscyamine as a hypnotic proved the presence of such peculiarities. In these experiments there occurred as accompanying manifestations, with a preparation of Buchner's, but few narcotic symptoms. After a preparation of Merck's they were more constant; sweating and mydriasis were frequently present. After Buchner's preparation the frequency of the pulse and respiration was lessened, and the temperature rose in the following night. As regards pulse, respiration, and temperature, Frommüller found no difference between it and morphia. After Merck's hyoscyamine mydriasis was constant, and once the frequency of the pulse rose unusually high in the night, and in one case there was even agitation and increase of motion after 0.006 gram.

Schroff noticed in himself after about 0.003 gram, dryness in mouth, pharynx, and larynx, slight mydriasis, diminution of a few beats of the pulse, fulness of head, dizziness, unsteadiness of gait; later a rise in the frequency of the pulse, and then quiet sleep; swallowing was difficult; the perception of taste and the sense of touch of the tongue were diminished.

Düllnberger took twice 0.002 gram. Whereupon the pulse sank at first, then increased in frequency, then followed fulness in the head, diminished salivation, dryness in mouth and throat, difficulty in swallowing, weakness, and mydriasis. After 0.005 mgram. there were diminished smell, taste, and headache, in addition to the symptoms of the smaller dose; in all cases there was an inclination to sleep, which was quiet and deep.

Rabbits die from 0.3 gram. twenty-four to forty-eight hours after of dyspnœa, acceleration of respiration, and mydriasis.

Binz says: Hyoscyamine (C_{15} H_{23} N O_3) (?) is a body chemically and physiologically allied to atropia. Owing to the differences in the preparations which have been hitherto used for experiment, it is impossible to say more. There is no proof of its inferiority to atropia.

Wood says: It has a very similar if not identical action with atropia. Indeed, at present it seems probable that the active principles of belladonna and hyoscyamus are really one alkaloid. Wood appears to doubt that hyoscyamine has a more powerful hypnotic effect than atropia.

Bartholow says: As atropia, daturia, and hyoscyamine are similar, if not identical, in chemical composition and in physiological action, the remarks already made in regard to the actions and uses of belladonna are applicable to stramonium and hyoscyamus.

The following conclusions, to which Oulmont and Laurent have been conducted, appear to the author (Bartholow) to be thoroughly well grounded:

1. Hyoscyamia and daturia act especially on the sympathetic nervous system.

2. In small doses they reduce the capillary circulation (contraction of the arterioles); in large doses they produce paralysis of the vessels (exhaust the irritability of the vasomotor system).

3. The arterial tension is increased by the administra-

tion of weak, and is diminished by powerful, doses. These effects are not modified by section of the vagi.

4. The frequency of the pulse is increased and its fulness diminished.

5. Hyoscyamia renders the movements of the heart regular; when applied directly it ultimately arrests the beats.

6. Both always accelerate the respiration.

7. Neither has any direct action on the nervous system of animal life.

Sensation and motor power are not modified by them. In toxic doses they blunt cutaneous sensibility.

8. These alkaloids have no action on the excitability of striated muscles; they do not modify their structure.

9. In small doses they accelerate the movements of the intestines; in large doses they paralyze them.

10. The general phenomena observed when these alkaloids are given are due to modification of the circulation, and disappear rapidly. The alkaloids are soon eliminated, especially by the urine, in which they may be found.

11. The dilatation of the pupil which is produced is due to stimulation of the sympathetic; the third pair of nerves is not concerned in its production.

12. Small doses generally give rise to slight increase of temperature; large doses diminish the central temperature.

Stillé and Maisch say in animals they cause dilatation of the pupil, and in full doses dryness of the mouth and a dull and lethargic condition, with loss of power in the hinder legs; in moderate doses they slow both respiration and circulation, rendering the pulse fuller and stronger; in full doses they have the opposite effect. They increase the discharge of urine.

On man the following effects are produced by henbane and hyoscyamia. The sense of touch is blunted, the voluntary muscles are apt to be cramped, or to be affected alternately with spasm and paralysis. No direct narcotic effect is produced in the greater number of cases; but rather a loquacious subdelirium, with hallucinations, which may merge into a restless and dreamy sleep. Only in large doses is it decidedly hypnotic. Its power to produce a peculiar talkative and pugnacious delirium was fully described by ancient writers. From an experimental point of view it must be concluded that, unless in very large doses, hyoscyamine is not so much a narcotic soporific as that it is anodyne or anæsthetic; that it excites the cerebral and depresses the spinal functions, and that it is mydriatic. Harley gives the following conclusions:

1st. Hyoscyamia differs somewhat from atropia in not accelerating the pulse as much, and by a greater effect on the cerebrum and the motor centres.

2d. Small doses will reduce the pulse rate by 10, or even 30 beats; larger doses cause a rise.

3d. Sleep and great muscular relaxation are produced.

4th. The action on the cerebrum is very similar to that of opium, except that it does not cause excitation of the motor centres. No antagonism exists between the two.

5th. It is excreted by the urine.

Lawson summarizes by saying:

1st. The smallest active doses when administered to animals cause numerical depression of the pulse, and increased arterial tension, reduce the temperature, dilate the pupil, and have little effect on the respirations.

Large doses elevate the pulse without previous depression, and this quickening is maintained for six or eight hours; great fall of temperature, diminution of respiration, loss of motor power, delirious excitement, and sometimes prolonged but interrupted sleep succeed, and are in their turn followed by sudden reduction of the pulse toward the initial point, and sometimes below it; this fall precedes complete recovery from the operation of the drug.

The drug usually causes increased urinary and diminished alvine secretion. In rabbits, pigeons, and others of the lower animals, hyoscyamine is almost, if not altogether, as active a poison as to man.

Long-continued use of the drug causes loss of weight, quickening of the pulsation with increase of arterial pressure, quickening also of respiration, and increase of temperature. Subsequently there is restoration of weight, but persistence of heightened pulsation, respiration, and temperature.

In man the cerebral symptoms are more marked than in the lower animals, and the motor, cardiac, respiratory, and thermal symptoms less so. With small doses the pulse is first slightly reduced, and at the commencement of the cerebral and motor excitement is elevated about 20 beats above the initial index. Nothnagel and Rossbach state that its action is similar to that of atropia.

This gives most of what is known about the physiological action of the drug. It is impossible for me to speak of each person who has written on this subject; a bibliography of the subject will be found at the end of this paper.

I will now proceed to the detail of my own personal experiments.

They were made in the physiological laboratory of Dr. Isaac Ott, Easton, Pennsylvania, and under his direction.

I always used Merck's preparation of hyoscyamine; the first experiments on frogs were made with the amorphous alkaloid, a brown, thick, syrupy-looking material of an oily feeling when rubbed between the fingers; later experiments on frogs were made with Merck's crystallized hyoscyamine; and all but one of the blood-pressure experiments and those on the muscles were made with the crystals.

It may be stated here that no difference was observed in the action of these preparations, except that the crystals were more rapid in action.

Experiment 1 (to determine the *general action* of the drug).—A large green frog, at 11.15 A.M., was given subcutaneously $\frac{1}{35}$ grain amorphous alkaloid hyoscyamine.

11.24 A.M., no special effect, so another $\frac{1}{35}$ grain is injected.

11.30 A.M., frog less energetic.

11.33 A.M., another $\frac{1}{35}$ grain is injected.

11.41 A.M., frog still jumps vigorously when irritated, but is disinclined to move; appears dull.

11.45 A.M., another $\frac{1}{35}$ grain injected.

At 11.50 A.M., no further change, so another $\frac{1}{35}$ grain is injected.

12.04 P.M., no further change. Another $\frac{1}{35}$ grain is injected, and at 12.05 another $\frac{1}{35}$ grain given.

At 12.10 P.M., the apathetic condition has increased, but frog still jumps with vigor when disturbed.

12.14 P.M., frog has ceased to jump when disturbed; if one hind leg be irritated he jerks it away, but makes no attempt to jump. Another $\frac{1}{35}$ grain is injected.

12.16 P.M., another $\frac{1}{35}$ grain injected.

12.19 P.M., slight muscular weakness of hind legs.

12.25 P.M., when frog is irritated, jumps away; is given another $\frac{1}{35}$ grain,and at 12.28 P.M. another $\frac{1}{35}$ grain injected.

12.34 P.M., another $\frac{1}{35}$ grain injected.

At 1.13 P.M., frog very much paralyzed. Muscles of leg twitch when irritated.

At 1.20 P.M., $\frac{1}{35}$ grain injected.

1.45 P.M., very much paralyzed; tries to draw away hind extremity when it is irritated, but does so only very little. Another $\frac{1}{35}$ grain injected.

3.30 P.M., frog has up to this time received $\frac{2}{5}$ of a grain of the alkaloid, and is now very much paralyzed, but still makes ineffectual efforts to move.

4.20 P.M., in same state; absolutely paralyzed everywhere; at night frog left completely paralyzed and stupid, one would think dead.

The next morning frog is found to have entirely recovered from the paralysis. Jumps about vigorously if touched; there has been no effect on the pupils at any time.

At 8.30 A.M. of the second morning, frog is found to have developed tetanus during the night ; legs are extended and body slightly arched backward ; touching the foot or a tap on the table near the frog throws all the muscles into tetanic convulsions ; in the afternoon this condition has increased to a tonic spasm, and when the feet are struck all the muscles are thrown into violent convulsions. Frog is found dead the next morning.

Experiment 2.—At 4 P.M., small black spotted frog given subcutaneously $\frac{1}{7}$ grain hyoscyamine.

At 4.11 P.M., another $\frac{1}{7}$ grain given.

At 4.20 P.M., frog very much paralyzed ; another $\frac{1}{7}$ grain injected ; no change.

4.35 P.M., another $\frac{1}{7}$ grain given ; frog left at night absolutely paralyzed and apparently dead.

8.30 A.M. next morning, frog still absolutely paralyzed, and at 10.25 A.M. another $\frac{1}{7}$ grain injected. Frog has now received $\frac{5}{7}$ grain hyoscyamine ; at night he is still absolutely paralyzed and apparently dead.

These experiments show that the alkaloid has a marked paralyzing effect ; it is now necessary to determine what this paralysis is due to—an action on the motor or sensory nerve or on the muscles. It is desired to kill a frog as rapidly as possible.

At 9.30 A.M., a small black-spotted frog has some of the amorphous alkaloid, without any dilution, injected subcutaneously, quantity unknown.

9.25 A.M., frog much paralyzed.

10.25 A.M., some disposition to oposthotonus.

10.30 A.M., more amorphous alkaloid injected (unknown quantity, about 4 or 5 drops).

12.15 P.M., completely paralyzed and in a stupid state ; sciatic exposed and tested with DuBois Raymond coil ; nerve is found irritable at 333 mm.

At 1.30 P.M., sciatic of the other leg is tested and found irritable at 60 mm. ; frog is apparently just dead.

Experiment 3.—Small green frog in which vessels of right leg have been ligated.

At 2.05 P.M. are given, dissolved in water, with one drop of muriatic acid, 1½ grains crystallized hyoscyamine, subcutaneously.

At 2.17 P.M., paralyzed in all extremities; on irritation of both hind legs they are drawn away, but the right leg (the one in which the vessels are ligated) much more than the left; the left leg is seldom moved on ordinary irritation, but a drop of sulphuric acid causes it to be jerked away violently; ordinary irritation causes movement of the leg in which the vessels have been tied, and no movement of the leg in which the vessels have not been tied.

At 3.45 P.M., sciatic nerve of the leg in which the vessels have been ligated is exposed and tested with DuBois Raymond coil and is found irritable at 180 mm., or, according to galvanometer scale, at 6° (Fick's method of graduation). The sciatic in which the vessels have been ligated is also tested and found irritable at 255 mm., or, according to galvanometer scale, at 2° (Fick's method).

These two experiments demonstrate a marked diminution in the irritability of the motor nerves and partial paralysis of them. The fact that the paralysis is not so great in the leg in which the vessels have been ligated as it is in the leg in which the vessels are not tied, indicates that the motor nerves must be poisoned by the alkaloid being carried to them in the blood supplied to the legs.

We now desire to determine if this paralysis of the motor nerves is peripheral or central.

Experiment 4.—Small green frog, in which the abdominal aorta was ligated.

At 2.45 P.M., was given, subcutaneously, 1½ grains crystallized hyoscyamine, dissolved in water, with one drop muriatic acid.

At 3 P.M. it is found that the front legs are very much paralyzed.

Experiment 5.—Green frog, in which the spinal arteries are ruptured and hyoscyamine is given subcutaneously, becomes paralyzed, as in frogs without any arteries having been ligated.

These experiments demonstrate that the paralysis of motor nerves is peripheral and not central.

REFLEX ACTION.

Experiment 6—Small green frog without spots, cerebrum separated from medulla, and, after sufficient time had elapsed to allow the irritation to subside, reflex irritability was tested with the sulphuric acid test; time taken on a metronome vibrating 100 beats a minute; the average beats are 18, at which the reflex is displayed; the frog is then given $\frac{1}{14}$ grain hyoscyamine crystals, subcutaneously; after a sufficient time the reflex excitability is tested and found as follows:

5.05	P.M.	26
5.10	"	45
5.15	"	57
5.20	"	40
5.25	"	45
5.30	"	46
6.00	"	36

Experiment 7.—Frog with spinal cord separated from medulla. Average beats 17. Subcutaneous injection of amorphous alkaloid hyoscyamine given; after a sufficient time had elapsed the reflex was taken with acid test.

3.50	P.M.	23
3.55	"	24
4.00	"	27
4.05	"	17
4.10	"	17
4.15	"	17
4.20	"	14
4.25	"	18
4.30	"	17
4.35	"	18

These two experiments taken together demonstrate a slight decrease in the reflex excitability.

SENSIBILITY.

Experiment 8.—Large green frog; blood-vessels of right leg ligated.

At 12.30 P.M., $\frac{1}{14}$ grain crystallized hyoscyamine injected subcutaneously.

At 1 P.M., appears to be equally sensitive in both legs.

1.20 P.M., frog becoming paralyzed, no difference in the sensibility of the two legs detected.

1.55 P.M., no disturbance of sensibility noted.

2.05 P.M., frog very much paralyzed; when put on his back is unable to turn over; there is no apparent difference in the sensibility of the two legs. This was the uniform result of all experiments made with regard to sensibility, and indicates that there is no material diminution of sensibility.

MUSCLES.

Experiment 9.—In the study of muscles the gastrocnemius of a frog was employed, and Marey's myograph; the contractions of the muscles registered on the drum of a Foucault regulator; the time of contractions taken with a tuning-fork. It was found that the alkaloid has no effect whatever on the muscles.

ACTION ON THE CIRCULATION.

These experiments were made on rabbits, usually of large size; the alkaloid was dissolved in water and injected into the jugular vein toward the heart; the arterial tension was registered by Ludwig's kymographion, and the time registered by an electro-magnet, and Ludwig's clock apparatus to break the current every second; the pulse and pressure are given for periods of fifteen seconds.

Experiment 10.—Large albino rabbit.

TIME.	PULSE.	PRESSURE.
2.15. 0 P.M.	47	108
2.15.15 "	$\frac{10}{35}$ grain H. injected.	
2.15.30 "	54	104
2.15.45 "	54	100
2.16. 0 "	54	100
2.16.15 "	50	120
2.16.30 "	53	120
2.16.45 "	56	120
2.17. 0 "	52	120
2.17.15 "	50	120
2.17.30 "	47	120
2.17.45 "	54	120
2.18. 0 "	51	120
2.18.15 "	52	120

TIME.	PULSE.	PRESSURE.
2.18.30 P.M.	45	116
2.18.45 “	48	116
2.23.30 “	52	120
2.28.45 “	54	112
2.29. 0 “	56	126
2.29.15 “	54 $\frac{10}{35}$ grain injected.	128
2.29.30 “	54	114
2.29.45 “	52	108
2.30. 0 “	51	108
2.30.15 “	56	112
2.30.30 “	52	118
2.30.45 “	52	116
2.31. 0 “	52	120
2.31.15 “	50	120
2.31.30 “	53	120
2.31.45 “	53	120
2.32. 0 “	50	120
2.32.15 “	56	120
2.38.45 “	50	116
2.39. 0 “	54 $\frac{10}{35}$ grain H. injected.	120
2.39.15 “	54	112
2.39.30 “	54	118
2.39.45 “	54	112
2.40. 0 “	50	114

Total amount of amorphous alkaloid hyoscyamine injected, $\frac{30}{35}$ grain.

Experiment 11.—In this experiment and all hereafter, crystallized hyoscyamia was used and always injected into the jugular vein toward heart.

Rabbit of large size.

TIME.	PULSE.	PRESSURE.
12. 0. 0 M.	55	104
12. 0.15 P.M.	41 $\frac{1}{35}$ grain H. injected.	108
12. 0.30 “	60	108
12. 0.45 “	64	100
12. 1. 0 “	67	104
12. 1.15 “	65	92

TIME.	PULSE.		PRESSURE.
12. 1.30 P.M.	59		92
12. 1.45 “	65		100
12. 2. 0 “	66		100
12. 2.15 “	66		104
12. 2.30 “	61		110
12. 2.45 “	62		110
12. 3. 0 “	62		100
12. 3.15 “	—		100
12. 3.30 “	63		112
12. 3.45 “	73		100
12. 4. 0 “	70		112
12. 4.15 “	70		110
12. 4.30 “	61		110
12. 4.45 “	67		116
12. 5. 0 “	68		116
12. 5.15 “	66		116
12. 5.30 “	68		108
12. 5.45 “	65		108
12. 6. 0 “	63		104
12. 6.15 “	66		104
12. 6.30 “	64		104
12. 6.45 “	64		104
12. 7 0 “	62		104
12. 7.15 “	63		104
12. 7.30 “	61		104
12.17. 0 “	64		106
12.17.15 “	71		106
12.17.30 “	66		106
12.17.45 “	67		110
12.18. 0 “	—		104
12.18.15 “	64		104
12.18.30 “	65		104
12.18.45 “	63	$\frac{1}{35}$ grain H. injected.	100
12.19. 0 “	66		104
12.19.30 “	—		102
12.19.45 “	65		104
12.20. 0 “	64		106
12.20.15 “	67		108
12.20.30 “	67		112
12.20.45 “	63		112
12.21. 0 “	67		106

TIME.		PULSE.		PRESSURE.
12.21.15	P.M.	66		108
12.21.30	“	—		106
12.21.45	“	65		104
12.25.30	“	58		102
12.37.45	“ interval of 12 minutes.	73		80
12.38. 0	“	60	Vagus irritated.	68
12.38.15	“	68		70
12.38.30	“	62		88
12.38.45	“	58		74
12.39. 0	“	56		70
12.39.15	“	63		80
12.40.30	“	60		72
2.52.45	“	65		70
2.53. 0	“	51	Vagus irritated.	62
2.53.15	“	56	Vagus irritated.	60
2.53.30	“	59		70
2.53.45	“	49		64
2.54. 0	“	54		68

Total amount of hyoscyamine given, $\frac{2}{35}$ grain. The first dose of hyoscyamine given was followed by an increase (104 to 108) of the blood pressure, and an increase in the number of arterial pulsations. Nineteen (19) minutes after the first injection was given another $\frac{1}{35}$ grain was injected. It is followed at once by a fall of the blood pressure, but no difference in the number of pulse beats; the blood pressure gradually sinks; and eighteen (18) minutes after the last injection, when the vagus is irritated with a current from DuBois Raymond coil, there is a slight fall in pulsation from 73 to 60; fifteen minutes after, when the vagus is again irritated there is again a slight fall in the pulsation from 65 to 51, and hereafter it continues to sink.

This experiment is decisive; it shows that hyoscyamine in large doses causes in the beginning increase of pulse and arterial tension, followed by a diminution of the blood pressure and a partial paralysis of the vagus, as strong electrical currents were used for nearly thirty seconds.

Experiment 12.—Large albino rabbit.

TIME.	PULSE.	PRESSURE.
4.15. 0 P.M.	70	106
4.15.15 "	60 (?)	110
4.15.30 "	64 $\frac{1}{7}$ grain H. injected	106
4.15.45 "	60	60
4.16. 0 "	65	44
4.16.15 "	65	42
4.16.30 "	59	50
4.16.45 "	66	56
4.17. 0 "	66	56
4.17.15 "	60	62
4.17.30 "	63	66
4.17.45 "	60 Vagus irritated	07
4.18. 0 "	—	82
4.18.15 "	—	76
4.18.30 "	—	80
4.18.45 "	—	80
4.19. 0 "	—	80
4.19.15 "	—	80
4.19.30 "	—	90

Upon the injection of the hyoscyamine, there was at once a very marked fall in the blood pressure and a slight diminution in the pulse rate, followed by a slight recovery in the blood pressure; toward the last the tracing was so indistinct that the pulse rate could not be ascertained. This experiment demonstrates that hyoscyamine partially paralyzes the vagi, as the pulse fell from 63 to 60. We desire now to discover, if after section of the vagi, hyoscyamine has any influence on pulse and blood pressure.

Experiment 13.—Rabbit of large size ; vagi cut.

TIME.	PULSE.	PRESSURE.
2.15. 0 P.M.	71	130
2.15.15 "	69	128
2.15.30 "	66	130

TIME.		PULSE.	PRESSURE.
2.15.45	P.M.	66 $\frac{1}{35}$ grain H. given	120
2.16. 0	"	65	128
2.16.15	"	66	120
2.16.30	"	68	120
2.16.45	"	67	114
2.17. 0	"	69	112
2.17.15	"	63 (?) Convulsive movement	124
2.17.30	"	76	120
2.17.45	"	77	120
2.22.45	"	77	120
2.23. 0	"	68	120
2.23.15	"	67	120
2.23.30	"	66	118
2.23.45	"	69	124
2.24. 0	"	72	116
2.24.15	"	60	116
2.24.30	"	70	114
2.24.45	"	71	114
2.25. 0	"	70	114
2.25.15	"	67	112
2.25.30	"	65	130
2.25.45	"	72	116
2.26. 0	"	72	120
2.26.15	"	71	118
2.26.30	"	72	120
2.26.45	"	61	118
2.27. 0	"	70	118
2.27.15	"	68	116
2.27.30	"	69	130
2.27.45	"	72	116
2.28. 0	"	69	118
2.32.15	"	—	120
2.32.30	"	69	114
2.32.45	"	72	116
2.33. 0	"	71	116
2.33.15	"	69	116
2.34.45	"	—	114
2.35. 0	"	69 $\frac{1}{35}$ grain injected	112
2.35.15	"	69	104
2.35.30	"	69	106
2.35.45	"	—	110

TIME.	PULSE.		PRESSURE.
2.36. 0 P.M.	—		112
2.36.15 “	70		116
2.36.30 “	71		112
2.36.45 “	71		114
2.37. 0 “	69		112
2.37.15 “	—		110
2.37.30 “	67		110
2.37.45 “	68	Convulsive movement	120
2.38. 0 “	71		114
2.38.15 “	67		114
3.41.45 “	60		112
3.42. 0 “	58		112
3.47.45 “	65		112
3.48. 0 “	65		110

This experiment indicates that after section of the vagi there is a slight increase, for a time, in the pulsations, and a fall of arterial tension. To eliminate the inhibitory action of the vagus, atropine was employed, and the effect of hyoscyamine studied.

Experiment 14.—Large albino rabbit; given an injection of atropine thirty-one (31) minutes after tracings were begun.

TIME.	PULSE.		PRESSURE.
1.30.15 P.M.	62		92
1.30.30 “	58		92
1.30.45 “	58		90
1.31. 0 “	55		92
1.31.15 “	52		90
1.31.30 “	61		90
1.31.45 “	56		100
1.32. 0 “	58		92
1.32.15 “	57	$\frac{1}{7}$ grain H. injected	92
1.32.30 “	53		92
1.32.45 “	59		88
1.33. 0 “	56		92
1.33.15 “	59		96
1.33.30 “	59		100
1.33.45 “	58		92

TIME.	PULSE.	PRESSURE.
1.34. 0 P.M.	58	94
1.34.15 "	65	94
1.34.30 "	60	94
1.34.45 "	61	112
1.35. 0 "	55	100
1.35.15 "	61	100
1.35.30 "	73	108
1.35.45 "	55 Sciatic irritated	118
1.36. 0 "	64 Sciatic irritated	148
1.36.15 "	68	120
1.36.30 "	62	112
1.36.45 "	62	110
1.37. 0 "	61	120
1.37.15 "	60	120
1.37.45 "	60	110
1.38. 0 "	62	106
1.41.45 "	61	100
1.47.15 "	66	92
1.47.30 "	67	96
1.47.45 "	63	100
1.48. 0 "	64	100
1.54.30 "	61	100

In this experiment, the vagi having been previously paralyzed with atropia, the injection of hyoscyamine produces but little effect that could be ascribed to hyoscyamia.

The irritation of the sciatic causing a rise in the blood pressure indicates that the vaso-motor system is still irritable

Experiment 15.—Large gray rabbit; all the nerves going to the heart divided in the neck. Medulla divided between occiput and atlas; artificial respiration instituted.

TIME.	PULSE.	PRESSURE.
3.15. 0 P.M.	65	66
3.15.15 "	66	64
3.15.30 "	67 $\frac{1}{35}$ grain H. injected	60
3.15.45 "	70	66
3.16. 0 "	68	60

TIME.	PULSE.	PRESSURE.
3.16.15 P.M.	74	60
3.16.30 "	68	60
3.16.45 "	67	56
3.17. 0 "	74	56
3.17.15 "	72	76
3.17.30 "	69	56
3.19.15 "	67	40
3.19.30 "	69	40
3.26. 0 "	69	36
3.26.15 "	68	36
3.26.45 "	69	34
3.27. 0 "	75	34
3.31.45 "	64	30
3.32. 0 "	66	30

In this experiment, after division of all the nerves going to the heart, any effect observed after injection of the drug must be due to its action on the ganglia in the heart or on the cardiac muscle.

The tracings show an increase of pulsations from the injection of hyoscyamine, and no rise of blood pressure, except momentarily; the gradual diminution in the blood pressure is due to the section removing the monarchial vaso-motor centre.

ACTION ON RESPIRATION.

Studied with the aid of Marey's polygraph and Marey Foucault regulator.

Experiment 16.—Large albino rabbit.

TIME.	RESPIRATIONS.	
3.30. 0 P.M.	15	
3.30.15 "	17	
3.30.30 "	14	
3.30.45 "	14	
3.31. 0 "	13	
3.31.15 "	15	
3.31.30 "	16	$\frac{1}{35}$ grain H. injected.

TIME.		RESPIRATIONS.
3.31.45	P.M.	18
3.32. 0	"	17
3.32.15	"	17
3.32.30	"	17
3.32.45	"	17
3.33. 0	"	20
3.33.15	"	18
3.33.30	"	18
3.33.45	"	18
3.34. 0	"	18
3.37. 0	"	19

This experiment shows a very slight increase in the number of respirations.

Experiment 17.—Large albino rabbit; vagi cut.

TIME.		RESPIRATIONS.	
4.15. 0	P.M.	9	
4.15.15	"	8	
4.15.30	"	9	$\frac{1}{35}$ grain H. injected.
4.15.45	"	9	
4.16. 0	"	10	
4.16.15	"	10	
4.16.30	"	9	
4.16.45	"	9	
4.17. 0	"	9	
4.17.15	"	10	
4.17.30	"	9	
4.17.45	"	9	
4.18. 0	"	9	
4.18.15	"	9	
4.18.30	"	9	
4.18.45	"	9	
4.19. 0	"	9	
4.21.45	"	10	
4.22. 0	"	9	
4.22.15	"	10	
4.22.30	"	9	
4.27.45	"	10	
4.28. 0	"	9	

TIME.		RESPIRATIONS.
4.28.15	P.M.	9
4.28.30	"	9
4.35. 0	"	9
4.35.15	"	9
4.35.30	"	8
4.35.45	"	10
4.36. 0	"	8

This experiment demonstrates that after section of the vagi hyoscyamine produces no effect on the respiration; hence the increase in respiratory movements must be due to stimulation of the centres of respiration.

These experiments demonstrate that:

1. Hyoscyamine causes paralysis if taken in sufficient dose; that this loss of motor power is due to paralysis of the motor nerves.

2. It exercises no visible effect on sensibility.

3. It has no effect on the muscles.

4. It decreases reflex excitability and afterward increases it; it tetanizes by an action on the spinal cord, acting in this respect like atropine.

5. In the beginning it causes a rise of pulse and arterial tension, which finally is followed by a fall of both.

Section of the vagi does not prevent either the preliminary rise of pulse rate or its subsequent fall.

6. After the use of atropine the changes produced by hyoscyamine in pulse rate are not in any way characteristic.

7. Irritations of the vagi reduce the pulse rate, but it is small compared with what normally takes place, so that it is inferred hyoscyamine partially paralyzes the inhibitory fibres of the vagi.

8. The increase of pulse rate is due to a partial paralysis of the inhibitory fibres of the vagi; the fall, to an action on the heart itself.

9. The rise of arterial tension is due to a stimulation of the monarchial vaso-motor centre; the rise is trifling after section of the medulla between atlas and occiput.

10. The fall of pressure is due to partial paralysis of the main vaso-motor centre, and probably to an action on the heart itself.

(*To be continued.*)